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(54) **Therapeutic compositions for intranasal administration which include ketorolac TM.**

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WO-A-90/01322
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DRUG METABOLISM & DISPOSITION, vol. 15, no. 5, 1987; E.J. MROSZCZAK et al., pp. 616-626

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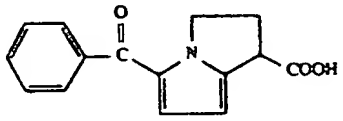
Description

Field of the Invention

This invention relates to therapeutic compositions with analgesic and anti-inflammatory activity, suitable for intranasal administration, which include Ketorolac™ or its salts as the active ingredient.

Background of the Invention

Ketorolac™ or 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1- carboxylic acid, the formula of which is:



is a product which has been known for several years (US Patent No. 4,089,969) and is used in human therapy as an analgesic and an anti-inflammatory.

The racemic form and the dextro and levo forms are known. Many pharmaceutically acceptable salts, the most commonly used of which is the tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) salt, are also known.

Hereinafter, the name Ketorolac™ shall always mean the racemic or optically active acid, as well as, specifically, its tromethamine salt or any other pharmaceutically acceptable salts.

Ample literature is available on Ketorolac™ (see, for instance, "Ketorolac™ - A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic potential", Drugs 39 (1): 86-109, 1990 - ADIS Press Limited) which is described as a drug with considerably higher analgesic and anti-inflammatory activity than many other non-steroid anti-inflammatory drugs. Its higher analgesic activity than morphine, of which it does not have the well known side effects, is of particular interest.

In the several pharmacological and clinical trials conducted with Ketorolac™, this drug was administered both by the oral route and by injection (intravenous and intramuscular), proving to be active and comparatively more active, by any route of administration, than the better known non-steroid drugs with analgesic and anti-inflammatory activity.

However, a percentage of about 10% of the patients treated by the intramuscular route showed undesirable side effects such as somnolence, local pain, sweating, nausea, headache, dizziness.

The incidence of side effects was even higher (around 32%) in the patients treated with Ketorolac™ by the oral route for a few days.

In the case of oral administration, gastrointestinal disorders appeared in up to 50% of the patients in addition to the above disorders. To date, intravenous administration has been tested in a limited way and, therefore, no sufficient data are available on tolerance.

On the whole, the data available to date clearly describe a drug which is very interesting from the point of view of activity, but unsatisfactory from the point of view of side effects.

Detailed Description of the Invention

We have now found that it is possible to prepare compositions containing Ketorolac™ as active ingredient, which are suitable for intranasal administration and that Ketorolac™ so administered is rapidly and thoroughly absorbed giving therapeutic effects equivalent to those obtained by the intravenous route (acute treatments) or the intramuscular or oral routes (extended or chronic treatments), however without inducing severe side effects. In particular, what is most important, any possibility of gastrointestinal disorders is excluded, while disorders caused by CNS stimulation are considerably reduced in number of patients affected and intensity.

As is known, news of intranasal administration of drugs have been published since 1980. At present, however, the molecules which have proved suitable for this route of administration are still very few: essentially only small molecules of peptides and insulin in special formulations. The ability of drug molecules to be absorbed by the nasal mucous membranes is utterly unpredictable, but above all it is the ability of drugs not to irritate the mucous membranes which is unpredictable. Mucous membrane irritation is

the most common reason of intranasal administration impracticability.

The new compositions according to the invention include the active ingredient in quantities ranging from 0.5 to 40 mg per dose, preferably 2 to 20 mg per dose, diluted in excipients which perform the functions of humectants, isotoning agents, antioxidants, buffers, preservatives.

A calcium chelating agent is also preferably included.

Dilution is such as to result in formulations with Ketorolac™ concentrations ranging from 5 to 20%, preferably from 10 to 15% weight/volume.

Of course, the selection of the supporting substances depends on the desired formulation dosage form, i.e. whether a solution to be used in drops or as a spray is desired or a suspension, ointment or gel to be applied in the nasal cavity are desired. In any case, it is possible to have single-dose packagings, which ensure application of an optimum quantity of drug.

Administration of the present intranasal formulations provides a good absolute bioavailability of Ketorolac™, as demonstrated in tests involving rabbits. The predictive value based on the rabbit model with respect to bioavailability of nasally administered Ketorolac™ in humans is known in the state of the art (Mroszczak, E.J. et al., Drug Metab. Dispos., 15:618-626, 1987, especially Tables 1 and 3). According to the results of the rabbit tests set forth below it has been extrapolated that in humans intranasal administration of a composition according to the invention in amounts ranging between 0.5 mg/kg/day and 4 mg/kg/day will generate plasma levels of Ketorolac™ within the range of 0.3-5 mg/liter of plasma.

Vehicles suitable for preparing the formulations according to the invention include aqueous solutions containing an appropriate isotoning agent selected among those commonly used in pharmaceutics.

Substances used for this purpose are, for instance, sodium chloride and glucose. The quantity of isotoning agent must be such as to provide a vehicle which, taking into account the osmotic effect of the active ingredient, has an osmotic pressure similar to that of biological fluids, generally from 150 to 850 milliOsmoles (mOsm) preferably from 270 to 330 mOsm.

However, it is known that the nasal mucous membrane is also capable of tolerating slightly hypertonic solutions. Should a suspension or gel be required instead of a solution, appropriate oily or gel vehicles may be used or one or more polymeric materials - some of which are capable of conferring bioadhesive characteristics to the vehicle - may be included in the formulation.

There are several polymers used in pharmaceutics for the preparation of a gel; the following can be mentioned as examples: hydroxypropyl cellulose (Klucel™), hydroxypropyl methyl cellulose (Methocel™), hydroxyethyl cellulose (Natrosol™), sodium carboxymethyl cellulose (Blanose™), acrylic polymers (Carbopol™, Polycarbophil™), gum xanthan, gum tragacanth, alginates, agar-agar.

Some of them, such as sodium carboxymethyl cellulose and acrylic polymers, have marked bioadhesive properties.

Other formulations suitable for the intranasal administration of Ketorolac™ are obtained adding to the aqueous vehicle polymers capable of changing the rheologic behaviour of the composition in relation to the temperature. These polymers make it possible to obtain low viscosity solutions at room temperature, which can be applied for instance by nasal spray and which, because of increased viscosity at body temperature, give a fluid which ensures a better and longer contact with the nasal mucous membrane. Polymers of this class are for instance polyoxyethylene- polyoxypropylene block copolymers (Poloxamer™).

In addition to aqueous, oily of gel vehicles, other vehicles which may be profitably used in the compositions according to the invention are solvent systems made up of ethyl alcohol, isopropyl alcohol, propylene glycol, polyethylene glycol, mixtures thereof or mixtures with water.

In any case, a buffer capable of modifying the pH should be present in order to create optimum conditions as far as product stability and tolerance are concerned (with pH range from 4 to 8, preferably from 5.5 to 7.5).

Other important excipients are absorption promoters which help product absorption by the nasal mucous membrane. These include chelating agents, fatty acids, bile acid salts and other surfactants, fusidic acid, lysophosphatides, cyclic peptide antibiotics, preservatives, carboxylic acids (ascorbic acid, amino acids), glycyrrhetinic acid, o-acylcarnitine. In this respect, diisopropyladipate, POE(9) lauryl alcohol, sodium glycocholate and lisophosphatidylcholine proved to be particularly active.

Finally, it is important for the new compositions according to the invention to contain preservant systems which ensure the microbiological stability of the active ingredient. Suitable preservants are, for instance, methyl paraoxybenzoate, propyl paraoxybenzoate, sodium benzoate, benzyl alcohol, benzalkonium chloride, chlorobutanol.

As indicated initially, the liquid Ketorolac™ formulations, preferably in the form of solutions, may be administered in the form of drops or spray, using atomisers equipped with a mechanical valve and possibly including a propellant of a type available in the market, such as butane, N_2, Ar, CO_2, nitrous oxide, propane,

dimethyl ether, chlorofluorocarbons (e.g. FREON) etc. Vehicles suitable for spray administration are water, alcohol, glycol and propylene glycol, used alone or in a mixture. Generally, illustrative formulations will contain the following ingredients and amounts (weight/volume):

Ingredient	Broad range(%)	Preferred range(%)
Na_2 EDTA (chelating agent)	0.001 - 1	0.05 - 0.1
Nipagin (preservative)	0.01 - 2	0.05 - 0.25
POE (9) lauryl alcohol (promotor)	0.1 - 10	1 - 10
NaCMC	0.1 - 5	0.3 - 3
Carbopol 940	0.05 - 2	0.1 - 1.5
Glycerol	1 - 99	
Sodium glycocholate	0.05 - 5	0.1 - 1

It is known, that ingredients such as sodium carboxymethyl cellulose and Carbopol exist in many different types depending on viscosity.

Their amounts are to be adjusted accordingly. Different adjustments to each formulation may also be necessary including omission of some optional ingredients and addition of others. It is thus not possible to give an all-encompassing amount range for each ingredient, but the optimization of each preparation according to the invention is within the skill of the art.

A possible, although not preferred, alternative for the intranasal application of the new Ketorolac™-based compositions comprises for a suspension of finely micronised active ingredient (generally from 1 to 200 μm preferably from 5 to 100 μm) in the propellant or in an oily vehicle or in another vehicle in which the drug is not soluble.

The vehicle is mixed or emulsified with the propellant. Vehicles suitable for this alternative are, for instance, vegetable and mineral oils and triglyceride mixtures. Appropriate surfactants, suspending agents and diluents of normal use in pharmaceutics must be added to these vehicles. Surfactants include without limitation sorbitan sesquioleate, sorbitan monooleate, sorbitan trioleate (amount, between 0.25 and 1%); suspending agents include without limitation isopropylmyristate (amount: between 0.5 and 1%) and colloidal silica (amount: 0.1 and 0.5%) and diluents include without limitation zinc stearate (between 0.6 to 1%).

To explain, but not limit, the invention, we report the following examples of formulations for the intranasal administration of Ketorolac™.

Example 1:

Composition	**%**	**for 10 liters**
Ketorolac™ tromethamine	5	500 g
EDTA disodium	0.01	1 g
Nipagin	0.1	10 g
Purified water, q.s. to	100	10 l

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 l of purified water and heat to a temperature of 80 • C.

Dissolve nipagin and EDTA disodium.

Stir the solution constantly to complete dissolution of the components.

Cool the obtained solution to room temperature.

Dissolve Ketorolac™ tromethamine by stirring.

Bring to volume with water.

The isotonicity of this composition is 190 mOsm but can be adjusted e.g. to 270 mOsm by the addition of 0.3% NaCl or 2,03% of glucose.

Example 2:

Composition	%	for 10 liters
Ketorolac™ tromethamine	5	500 g
POE (9) lauryl alcohol	5	500 g
Nipagin	0.1	10 g
EDTA disodium	0.01	1 g
Purified water, q.s. to	100	10 l

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 l of purified water and heat to a temperature of 80 • C.

Dissolve nipagin and EDTA disodium.

Stir the solution constantly to complete dissolution of the components.

Cool the obtained solution to room temperature.

Add POE (9) lauryl alcohol and stir to complete dissolution.

Dissolve Ketorolac™ tromethamine by stirring.

Bring to volume with water.

Example 3:

Composition	%	for 10 liters
Ketorolac™ tromethamine	5	500 g
Sodium carboxymethyl cellulose	1	100 g
Tromethomine, q.s. to pH = 6		
Nipogin	0.1	10 g
Purified water, q.s. to	100	10 l

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 l of purified water and heat to a temperature of 80 • C.

Dissolve nipagin.

Cool the obtained solution to room temperature.

Dissolve Ketorolac™ and continue stirring to complete dissolution of the drug.

Disperse sodium carboxymethyl cellulose in the solution stirring vigorously.

Continue stirring to complete hydration of the polymer. Adjust the pH to the required value by suitably adding tromethamine dissolved in water.

Bring to volume with water.

Example 4:

Composition	%	for 10 liters
Ketorolac™ tromethamine	5	500 g
Nipagin	0.1	10 g
EDTA disodium	0.01	1 g
Carbopol 940	0.1	10 g
Tromethamine, q.s. to pH = 7-7.4		
Glycerol	2	200 g
Purified water, q.s. to	100	10 l

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 4 l of purified water and heat to a temperature of 80 °C.

Dissolve nipagin and EDTA.

Cool the solution to room temperature.

Dissolve Ketorolac™ tromethamine.

Complete the dissolution of the active ingredient and adjust the pH to a value of 7.1-7.4 by adding a 5% tromethamine solution.

In a separate vessel equipped with mixer, introduce the quantity of glycerol called for in the formulation. Introduce Carbopol and mix until a homogeneous dispersion in the glycerol is obtained.

Add 4 l of purified water with vigorous stirring and continue stirring the solution to complete hydration of the polymer.

Combine the solution containing the active ingredient and the polymer solution with stirring.

If necessary, adjust the pH to the required value with the tromethamine solution.

Bring to volume with water.

Example 5:

Composition	%	for 10 liters
Ketorolac™ tromethamine	5	500 g
Lutrol F127	17	1.7 Kg
EDTA disodium	0.01	1 g
Nipagin	0.1	10 g
Purified water, q.s. to	100	10 l

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 4 l of purified water and heat to a temperature of 80 °C.

Dissolve nipagin and EDTA disodium.

Cool the solution to 4 °C and then, maintaining it between 4 and 6 °C throughout the operation, gradually add Lutrol F127 with stirring.

Continue stirring to complete hydration of the polymer.

Bring the solution to room temperature.

Dissolve Ketorolac™ tromethamine.

Bring to volume with water.

Example 6:

Composition	%	for 10 liters
Ketorolac™ tromethamine	5	500 g
NaCMC	2	200 g
EDTA disodium	0.01	1 g
Nipagin	0.1	10 g
Purified water, q.s. to	100	10 l

The procedure of Example 3 was used to make the above formulation adding EDTA during the solubilization of nipagin
and except that no tromethamine was added.

Example 7:

Composition	%	for 10 liters
Ketorolac™ tromethamine	5	500 g
Lutrol F127	15	1500 g
EDTA disodium	0.01	1 g
Nipagin	0.1	10 g
Purified water, q.s. to	100	10 l

The procedure of the Example 5 was used to make the above formulation.

Example 8

Composition	%	for 10 liters
Ketorolac™ tromethamine	5	500 g
EDTA disodium	0.01	1 g
Nipagin	0.1	10 g
Sodium glycocholate	0.3	30 g
Purified water, q.s. to	100	10 l

The procedure of Example 1 was used except that sodium glycocholate was dissolved with the nipagin and disodium EDTA at 80 °C in water.

The isotonicity of this composition was 190 mOsm; it can be adjusted e.g. to 330 mOsm by the addition of 0.44% NaCl or 3.05% glucose.

Example 9

Composition	%	for 10 liters
Ketorolac™ tromethamine	5	500 g
Lutrol F127	15	1500 g
Sodium glycocholate	0.3	30 g
EDTA disodium	0.01	1 g
Nipagin	0.1	10 g
Purified water, q.s. to	100	10 l

The procedure of Example 5 was used except that sodium glycocholate was dissolved with nipagin and disodium EDTA at 80 °C.

Example 10

The authors studied the stability of the preparations described in the Examples 1, 2, 6, 7, 8 and 9. The storing conditions were 4 °C, 22 °C, 45 °C and 55 °C. The authors analyzed the preparations at the beginning of the storing period and after 1, 2, 3 and 6 months. UV and HPLC analysis has been used.

The parameters tested were:

- content of active compound (UV and HPLC);
- content of keto and hydroxy degradation products (UV and HPLC);
- appearance and color (visual examination);
- pH (digital pH meter).

The results are summerized in Table 1.

TABLE 1

Example	Temp. °C	Months	KTM (mg/ml)	Keto %	Hydroxy %	Appearance of solution	pH
1	22	0	50.1	0.8	0.3	light yellow	6.2
	45	2	50.8	0.2	0.0	yellow	6.5
	45	3	49.6	0.2	0.0	opalescent yellow	6.5
	45	6	51.4	0.4	0.0	yellow with deposit	6.5
2	22	0	49.0	0.1	0.3	light yellow	6.4
	45	2	47.7	0.4	0.0	yellow	6.8
	45	3	46.7	0.2	0.0	yellow	6.9
	45	6	47.3	1.0	0.0	yellow	7.0
6	22	0	49.6	0.1	0.4	yellow	6.0
	45	1	47.0	0.1	0.1	yellow	6.5
	45	3	48.8	0.2	0.0	yellow	6.5
	45	6	50.1	0.9	0.0	yellow with deposit	5.5
7	22	0	48.5	0.0	0.5	light yellow	6.7
	55	1	49.0	0.8	0.0	yellow	6.8
	55	3	47.1	1.4	1.9	orange	6.6
8	22	0	52.3	0.0	0.0	light yellow	6.2
	45	1	53.2	0.0	0.0	yellow	6.4
	45	3	54.3	0.5	0.0	yellow	6.5
9	22	0	48.7	0.0	0.0	light yellow	6.7
	45	1	51.7	0.0	0.0	yellow	6.8
KTM = Ketorolac™ tromethamine							

Example 11

The authors tested in vitro the thermosetting properties of some preparations (Examples 1, 2, 7, 9). A standardized amount of every preparation has been sprayed to a 37 °C costant-temperature, vertical glass surface and the time that the drops of preparation spent to cover 10 cm has been measured. The speed of solution in moving on the constant-temperature surface is an indicator of the thermosetting properties of the dosage form. Examples 7 and 9 gave the best results in therms of thermosetting properties.

The results are reported in Table 2.

TABLE 2

Preparation time to cover 10 cm.	
H_2O	3 sec.
Example 1	3 sec.
Example 2	3 sec.
Example 7	12 sec.
Example 9	15 sec.

Example 12:

The authors have studied the nasal absortion and the local tolerance of four preparations (Examples 1, 6, 8, 9) in White New Zealand rabbits (three rabbits for each experimental group plus three controls). Each rabbit received an active preparation in one nostril and its placebo in the other. Each animal received 2 mg/kg of Ketorolac™ tromethamine (KTM), twice a day for seven days and once on the eighth day. The control rabbits were treated, after seven days of nasal administration of physiologic solution, with 2 mg/kg of KTM by intravenous route. After the last treatment plasma samples were collected at several times and KTM plasma levels were investigated by HPLC. After the last blood sample was drawn all the animals were sacrified by excision of femoral arteries, after having been completely anaesthetized. Nasal turbinates , larynx and pharynx were removed and subjected to histological examination.

Pharmacokinetic parameters are reported in Tables 3, 4, 5, 6, 7.

The local (nasal mucous) tolerance data showed good tolerance of the Ketorolac™-containing intranasal preparations with the formulation of Example 1 being the best tolerated followed by that of Example 6, Example 9 and Example 8 in that order.

Table 3

Control Absorption of KTM

Route of Administration: Intravenous

Administered Dose: 2 mg/kg

Plasma Concentration of KTM as ng/ml

Sampling Time (hours)	Mean (ng/ml)	± S.D.
0	0	0
0.083	14510	1999
0.25	7682	2887
0.5	3884	1891
1	1703	792
2	403	167
3	120	67
5	20	7

Table 4

Nasal Absorption of KTM

Composition: Example 1

Route of Administration: Intranasal

Administered Dose: 2 mg/kg/administration

Sampling Time (hours)	Mean (ng/ml)	± S.D.
0	18	16
0.25	2363	1035
0.5	1875	726
1	1103	490
2	593	217
3	267	55
5	121	52

Table 5

Nasal Absorption of KTM

Composition: Example 8

Route od Administration: Intranasal

Administration Dose: 2 mg/kg/administration

Sampling Time (hours)	Mean (ng/ml)	± S.D.
0	29	22
0.25	2973	1258
0.5	2654	880
1	2246	1145
2	1121	832
3	665	444
5	427	194

Table 6

Nasal Absorption of KTM

Composition: Example 9

Route of Administration: Intranasal

Administered Dose: 2 µg/kg/administration

Sampling Time (hours)	Mean (ng/ml)	± S.D.
0	35	17
0.25	2036	572
0.5	1663	778
1	1009	345
2	325	103
3	184	22
5	198	52

Table 7

Nasal Absorption of KTM

Composition: Example 6

Route of Administration: Intranasal

Administered Dose: 2 µg/kg/administration

Sampling Time dei campioni (ore)	Mean (ng/ml)	± S.D.
0	23	20
0.25	1872	1228
0.5	1772	1027
1	1213	619
2	616	293
3	269	96
5	133	23

From the foregoing data, the following bioavailability parameters were calculated:

Table 8

Formulation	i.v.	Example 1 (A)	Example 8 (B)	Example 9 (C)	Example 6 (D)
		AUC_{0-5} (h.ng/ml)			
average	7355	3237	5972	2692	3197
+/- S.D.	2405	1129	2973	571	976
CV (%)	32.7	34.9	49.8	21.2	30.5
		T_{max} (ore)			
average		0.25	0.42	0.33	0.33
+/- S.D.		0	0.14	0.14	0.14
CV (%)		0	34.6	43.3	43.3
		C_{max} (ng/ml)			
average		2363	3226	2229	1895
+/- S.D.		1035	1079	335	1203
CV (%)		43.8	33.4	15.0	63.5
		AUC i.n. / AUC i.v.			
average		0.44	0.81	0.36	0.43

i.n. = intranasal
i.v = intravenous
AUC_{0-5} = Total area under the curve (AUC) of the concentration-time profile from time 0 to 5.

Each value is the mean of the data obtained from three animals.

The foregoing results indicate that intranasal formulations of Ketorolac™ according to the invention are compared favorably with intravenous formulations in terms of absorption (Formulation B from Example 8 being the best absorbed), time to maximum plasma concentration, and exhibit good absolute bioavailability (specially formulation B).

Example 13

Composition	%	for 10 liters
Ketorolac™ tromethamin	15	1500 g
EDTA disodium	0.01	1 g
Nipagin	0.2	20 g
Purified water, q.s. to	100	10 l

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80 °C.
Dissolve nipagin and EDTA disodium.
Stir the solution constantly to complete dissolution of the components.
Cool the obtained solution to room temperature.
Dissolve Ketorolac™ tromethamine by stirring.
Bring to volume with water.

Example 14

Composition	%	for 10 liters
Ketorolac™ tromethamine	15	1500 g
EDTA disodium	0.01	1 g
Nipagin	0.2	20 g
Glycocholic acid	0.3	30 g
Purified water, q.s. to	100	10 l

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80 °C.
Dissolve nipagin and EDTA disodium.
Stir the solution constantly to complete dissolution of the components.
Cool the obtained solution to room temperature.
Dissolve Ketorolac™ tromethamine and glycocholic acid by stirring.
Bring to volume with water.

Example 15

Composition	%	for 10 liters
Ketorolac™ tromethamine	15	1500 g
EDTA disodium	0.01	1 g
Nipagin	0.2	20 g
Glycocholic acid	0.3	30 g
Lutrol F127	15	1500 g
Purified water, q.s. to	100	10 l

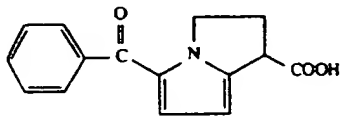
Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 8 liters of purified water and heat to a temperature of 80 °C.
Dissolve nipagin and EDTA disodium.
Stir the solution to 4 °C and then, maintaining it between 4 and 6 °C throughout the operation, gradually add Lutrol F127 with stirring.
Continue stirring to complete hydration of the polymer.
Bring the solution to room temperature.
Dissolv Ketorolac™ tromethamine and glycocholic acid.
Bring to volume with water.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. A therapeutic composition for intranasal administration which contains as the active ingredient 0.5-40 mg/dose of 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, the formula of which is:



in a racemic or optically active form, or any of its therapeutically acceptable salts, associated with appropriate excipients and diluents.

2. A therapeutic composition for intranasal administration according to claim 1, which contains 2-20 mg/dose of active ingredient.

3. A therapeutic composition for intranasal administration according to claim 1, which contains 5-20% of active ingredient.

4. A therapeutic composition for intranasal administration according to claim 3, which contains 10-15% of active ingredient.

5. A therapeutic composition for intranasal administration according to claim 1, in a single-dose form.

6. A therapeutic composition for intranasal administration according to claim 1, in the form of a solution or suspension.

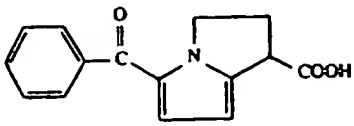
7. A therapeutic composition for intranasal administration according to claim 1, wherein excipients include bioadhesive polymers.

8. A therapeutic composition for intranasal administration according to claim 1, wherein excipients include at least one polymer capable of modifying vehicle viscosity based on temperature change.

9. A therapeutic composition for intranasal administration according to claim 1, wherein excipients include absorption promoters.

10. A therapeutic composition for intranasal administration according to claim 9, wherein said promoters comprise at least one of POE(9) lauryl alcohol and sodium glycocolate and lysophosphatidyl choline.

11. Use of a 0.5-40 mg/dose of 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, the formula of which is



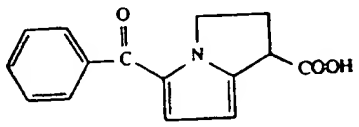
in the preparation of a therapeutic composition for intranasal administration which has an analgesic and anti-inflammatory activity.

12. A process for the preparation of a therapeutic composition with analgesic and anti-inflammatory activity, for intranasal administration, which includes mixing with appropriate excipients and diluents a 0.5-40 mg/dose of 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid in a racemic or optically active form

or of one of its therapeutically acceptable salts.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of a therapeutic composition, for intranasal administration containing as active ingredient a 0.5-40 mg/dose of 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, the formula of which is:



in a racemic or optically active form, or any of its therapeutically acceptable salts, associated with appropriate excipients and diluents, comprising mixing the active ingredient with said excipients.

2. Process according to claim 1, wherein said composition has an analgesic and anti-inflammatory activity.

3. Process according to claim 1, wherein said composition contains 2-20 mg/dose of active ingredient.

4. Process according to claim 1, wherein said composition contains 5-20% of active ingredient.

5. Process according to claim 5, wherein said composition contains 10-15% of active ingredient.

6. Process according to claim 1, wherein said composition is in a single-dose form.

7. Process according to claim 1, wherein said composition is in the form of a solution or suspension.

8. Process according to claim 1, wherein said excipients include bioadhesive polymers.

9. Process according to claim 1, wherein said excipients include polymers capable of modifying vehicle viscosity based on temperature change.

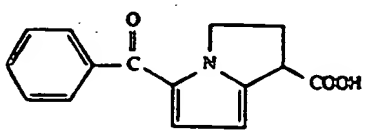
10. Process according to claim 1, wherein said excipients include absorption promoters.

11. Process according to claim 11, wherein said promoters comprise at least one of POE(9) lauryl alcohol, sodium glycocolate and lysophosphatidyl choline.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. Therapeutische Zusammensetzung zur nasalen Verabreichung, welche als aktiven Bestandteil 0,5 bis 40 mg/Dosis 5-Benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylsäure der Formel:



in einer razemischen oder optisch aktiven Form, oder eines ihrer therapeutisch verträglichen Salze, zusammen mit geeigneten Exzipienten und Verdünnungsmitteln, enthält.

2. Therapeutische Zusammenseztung zur intranasalen Verabreichung gemäß Anspruch 1, welche 2 bis 20 mg/Dosis aktiven Bestandteil enthält.

3. Therapeutische Zusammensetzung zur intranasalen Verabreichung gemäß Anspruch 1, welche 5 bis 20% aktiven Bestandteil enthält.

4. Therapeutische Zusammensetzung zur intranasalen Verabreichung gemäß Anspruch 3, welche 10 bis 15% aktiven Bestandteil enthält.

5. Therapeutische Zusammensetzung zur intranasalen Verabreichung gemäß Anspruch 1 in ener Einzeldosisform.

6. Therapeutische Zusammensetzung zur intranasalen Verabreichung gemäß Anspruch 1 in der Form einer Lösung oder Suspension.

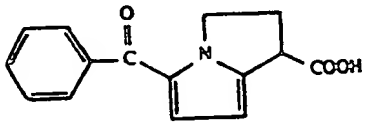
7. Therapeutische Zusammensetzung zur intranasalen Verabreichung gemäß Anspruch 1, worin die Exzipienten bioadhäsive Polymere einschließen.

8. Therapeutische Zusammensetzung zur intranasalen Verabreichung gemäß Anspruch 1, worin die Exzipienten mindestens ein Polymer einschließen, das dazu befähigt ist, die auf einen Temperaturwechsel bezogene Viskosität des Trägermittels zu modifizieren.

9. Therapeutische Zusammensetzung zur intranasalen Verabreichung gemäß Anspruch 1, worin die Exzipienten Absorptionspromotoren einschließen.

10. Therapeutische Zusammensetzung zur intranasalen Verabreichung gemäß Anspruch 9, worin die genannten Promotoren mindestens eine Verbindung aus POE(9)-Laurylalkohol und Natriumglycocholat und Lysophosphatidylcholin umfassen.

11. Verwendung von 0,5 bis 40 mg/Dosis 5-Benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylsäure der Formel:

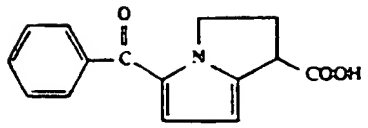


zur Herstellung einer therapeutischen Zusammensetzung zur intranasalen Verabreichung, welche eine schmerzstillende und entzündungshemmende Wirksamkeit aufweist.

12. Verfahren zur Herstellung einer therapeutischen Zusammensetzung mit schmerzstillender und entzündungshemmender Wirksamkeit zur intranasalen Verabreichung, wobei man 0,5 bis 40 mg/Dosis 5-Benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylsäure, die in razemischer oder optisch aktiver Form vorliegt, oder eines ihrer therapeutisch verträglichen Salze mit geeigneten Exzipienten und Verdünnungsmitteln vermischt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer therapeutischen Zusammensetzung zur intranasalen Verabreichung, welche als aktiven Bestandteil 0,5 bis 40 mg/Dosis 5-Benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylsäure der Formel:



die in razemischer oder optischer Form vorliegt, oder eines ihrer therapeutisch verträglichen Salze, zusammen mit geeigneten Exzipienten und Verdünnungsmitteln, enthält, wobei man den aktiven Bestandteil mit den genannten Exzipienten vermischt.

2. Verfahren gemäß Anspruch 1, wobei die genannte Zusammensetzung eine schmerzstillende und entzündungshemmende Wirksamkeit aufweist.

3. Verfahren gemäß Anspruch 1, worin die genannte Zusammensetzung 2 bis 20 mg/Dosis aktiven Bestandteil enthält.

4. Verfahren gemäß Anspruch 1, worin die genannte Zusammensetzung 5 bis 20% aktiven Bestandteil enthält.

5. Verfahren gemäß Anspruch 4, worin die genannte Zusammensetzung 10 bis 15% aktiven Bestandteil enthält.

6. Verfahren gemäß Anspruch 1, worin die genannte Zusammensetzung in einer Einzeldosisform vorliegt.

7. Verfahren gemäß Anspruch 1, worin die genannte Zusammensetzung in der Form einer Lösung oder Suspension vorliegt.

8. Verfahren gemäß Anspruch 1, worin die genannten Exzipienten bioadhäsive Polymere einschließen.

9. Verfahren gemäß Anspruch 1, worin die genannten Exzipienten Polymere einschließen, die dazu befähigt sind, die auf einen Temperaturwechsel bezogene Viskosität des Trägermittels zu modifizieren.

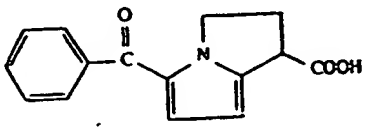
10. Verfahren gemäß Anspruch 1, worin die genannten Exzipienten Absorptionspromotoren einschließen.

11. Verfahren gemäß Anspruch 10, worin die genannten Promotoren mindestens eine Verbindung aus POE(9)-Laurylalkohol, Natriumglycocholat oder Lysophosphatidylcholin umfassen.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. Composition thérapeutique pour l'administration intranasale, qui contient comme ingrédient actif 0,5-40 mg/dose d'acide 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylique, dont la formule est:



sous forme racémique ou optiquement active, ou l'un quelconque de ses sels acceptables du point de vue thérapeutique, associé à des excipients et diluants appropriés.

2. Composition thérapeutique pour l'administration intranasale selon la revendication 1, qui contient 2-20 mg/dose d'ingrédient actif.

3. Composition thérapeutique pour l'administration intranasale selon la revendication 1, qui contient 5-20% d'ingrédient actif.

4. Composition thérapeutique pour l'administration intranasale selon la revendication 1, qui contient 10-15% d'ingrédient actif.

5. Composition thérapeutique pour l'administration intranasale selon la revendication 1, sous forme de dose unitaire.

6. Composition thérapeutique pour l'administration intranasale selon la revendication 1, sous forme d'une solution ou suspension.

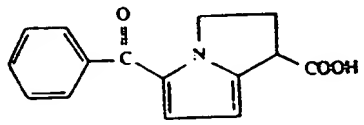
7. Composition thérapeutique pour l'administration intranasale selon la revendication 1, dans laquelle les excipients comportent des polymères bioadhésifs.

8. Composition thérapeutique pour l'administration intranasale selon la revendication 1, dans laquelle les excipients comportent au moins un polymère capable de modifier la viscosité de l'excipient en fonction de la variation de température.

9. Composition thérapeutique pour l'administration intranasale selon la revendication 1, dans laquelle les excipients comportent des promoteurs d'absorption.

10. Composition thérapeutique pour l'administration intranasale selon la revendication 9, dans laquelle lesdits promoteurs comportent au moins un composé choisi parmi l'alcool laurylique POE (9), le glycocolate de sodium et la lysophosphatidyle choline.

11. Utilisation de 0,5-40 mg/dose d'acide 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylique, dont la formule est:

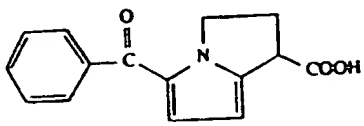


pour la préparation d'une composition thérapeutique pour l'administration intranasale, ayant une activité analgésique et anti-inflammatoire.

12. Procédé de préparation d'une composition thérapeutique ayant une activité analgésique et anti-inflammatoire, pour l'administration intranasale, qui comporte un mélange avec des excipients et diluants appropriés de 0,5-40 mg/dose d'acide 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylique sous une forme racémique ou optiquement active, ou de l'un de ses sels acceptables du point de vue pharmaceutique.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'une composition thérapeutique pour l'administration intranasale, qui contient comme ingrédient actif 0,5-40 mg/dose d'acide 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylique, dont la formule est:



sous forme racémique ou optiquement active, ou l'un quelconque de ses sels acceptables du point de

vue pharmaceutique, associés à des excipients et diluants appropriés, comprenant le mélange de l'ingrédient actif avec lesdits excipients.

2. Procédé selon la revendication 1, dans lequel ladite composition a une activité analgésique et anti-inflammatoire.

3. Procédé selon la revendication 1, dans lequel ladite composition contient 2-20 mg/dose d'ingrédient actif.

4. Procédé selon la revendication 1, dans lequel ladite composition contient 5-20% d'ingrédient actif.

5. Procédé selon la revendication 1, dans lequel ladite composition contient 10-15% d'ingrédient actif.

6. Procédé selon la revendication 1, dans lequel ladite composition est sous forme d'une dose unitaire.

7. Procédé selon la revendication 1, dans lequel ladite composition est sous forme d'une solution ou suspension.

8. Procédé selon la revendication 1, dans lequel lesdits excipients comportent des polymères bioadhésifs.

9. Procédé selon la revendication 1, dans lequel lesdits excipients comportent au moins un polymère capable de modifier la viscosité de l'excipient en fonction de la variation de température.

10. Procédé selon la revendication 1, dans lequel lesdits excipients comportent des promoteurs d'absorption.

11. Procédé selon la revendication 11, dans lequel lesdits promoteurs comportent au moins un élément choisi parmi l'alcool laurylique POE (9) le glycocolate de sodium et le lysophosphatidyle choline.